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Parkinson's Disease: A Case-Control Study of Occupational and Environmental Risk Factors

Clyde Hertzman, MD, MSc, FRCPC, Michele Wiens, MA, David Bowering, MD, MHSc, Barry Snow, MBChB, FRACP, and Donald Calne, DM, FRCP, FRCPC

We compared personal histories of 57 cases and 122 age-matched controls to identify possible environmental determinants of Parkinson's disease (PD). Odds ratios (OR) adjusted for sex, age, and smoking were computed using stepwise logistic regression. We found a statistically significant increased risk for working in orchards (OR = 3.69, p = 0.012, 95% CI = 1.34, 10.27) and a marginally significant increased risk associated with working in planer mills (OR = 4.11, p = 0.065, 95% CI = 0.91, 18.50). A Fisher's exact test of the association between PD development and (1) paraquat contact, and (2) postural tremor gave statistically significant probability estimates of 0.01 and 0.03, respectively. The relative risk of PD decreased with smoking, an inverse relationship supported by many studies.

Key words: Parkinson's disease, environmental exposure, occupational exposure, pesticides, toxins

INTRODUCTION

The etiology of Parkinson's disease (PD) remains unknown, despite the elapse of 150 years since the description of this disease [Parkinson, 1817]. The associations between PD development and various industrial and agricultural chemicals have stimulated speculation that PD may be caused by agents that occur in the environment [Barbeau et al., 1986; Tanner et al., 1987; Rajput et al., 1986; Calne and Langston, 1983]. MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) causes clinical and neuropathological parkinsonian symptoms in humans [Langston and Ballard, 1983] and has received considerable attention as a causative factor. This hypothesis has received further support in histochemical, autoradiographic, and primate studies [Burns et al., 1983; Javitch et al., 1985]. The metabolites of MPTP, MPDP+ (1-methyl-4 phenyl-2,3-dihydropyridinium) and MPP+ (1-methyl-4-phenylpyridinium) can damage neurons in the substantia nigra and result in PD [Langston and Ballard, 1983]. MPTP is chemically similar to some commonly used herbicides, such as paraquat, and MPP+ has been commercially marketed as a herbicide under the

Division of Occupational and Environmental Health, Department of Health Care and Epidemiology, University of British Columbia, Vancouver, B.C. (C.H., M.W.).
Skeena Health Unit, Terrace, B.C. (D.B.).
Division of Neurology, University of British Columbia, Vancouver, B.C. (B.S., D.C.).
Address reprint requests to Dr. C. Hertzman, Division of Occupational and Environmental Health, Department of Health Care and Epidemiology, Vancouver, B.C., Canada V6T 1W5.
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name cyperquat. Paraquat is widely used as a nonselective contact herbicide; any link between chemical agents and PD would therefore have serious public health implications. Attempts have been made to correlate PD prevalence with the use of pesticides and industrial activity. Barbeau et al. [1986] found a rank-order correlation of PD prevalence with the volume of pesticides sold in 6 hydrographic regions in Quebec, as well as a correlation between PD prevalence and heavy industry in the urban regions. The same group suggested that PD patients may be more likely to have a specific hydroxylation defect in the P450 enzyme system, which might inhibit their ability to metabolize toxins [Barbeau et al., 1985], yet this finding has been questioned [Comella et al., 1987]. Although paraquat penetrates the blood-brain barrier poorly, Endo et al. [1988] demonstrated a long-lasting reduction of catecholamines in the midbrain of mice after oral treatment of Gramoxon, a paraquat-containing herbicide.

Some investigators consider the stability of age-specific incidence of PD within regions over time to constitute evidence against an environmental association given increasing use of chemicals in recent decades [Vieregge et al., 1988]. However, this stability has occurred during the period of die-off of the postencephalitic cohort of PD, suggesting the possibility of a counteracting factor that maintains high incidence rates [Rajput, 1984]. Previous studies suggest that an increased risk is associated with the rural environment [Rajput et al., 1986] and that PD is more common in developed countries than in Third World countries [Cosnett and Bill, 1988; Li et al., 1985; Schoenberg et al., 1985]. To identify environmental factors relating to PD, we conducted a case-control study in a rural area of Canada with a high PD prevalence, in order to generate specific hypotheses that could be tested in future studies.

PATIENTS AND METHODS

We drew the study population from a mountainous rural area of British Columbia—an area with a population of 80,000 and with forestry, smelting, and agriculture as its economic base. We chose this region because the prevalence of PD was reportedly high [Rowe, 1982], the population was stable, and the area was geographically defined. We contacted all physicians in the area first by telephone, then by letter, and asked them to identify patients under their care with a diagnosis of PD who might respond to a postal questionnaire and submit to a clinical examination. As a supplement, we checked with neurologists' practices of the regional and provincial referral clinics for patients from the region. We had full cooperation from all physicians, and we do not believe any identities were withheld from us. By way of the questionnaire, we gathered information on the use of private well water, the past occupations of respondents since age 25, past handling of certain chemicals, and smoking. The questionnaire was effectively designed to be able to pick up exposures back into early adulthood. We completed a reliability check on the questionnaire answers approximately 1 month after they had been returned. This check involved contacting cases and every fifth control and reasking them 6 questions, which we selected from the questionnaire.

Of the 78 patients whose names we received from physicians, 6 chose not to complete the questionnaire, giving a response rate by cases of 92%. Subsequent to questionnaire completion, 2 patients died and 1 moved out of the area and could not be contacted further. The remaining 69 formed the sample population. To ascertain

TABLE I. Crude Odds Ratios; Case-Control Study of Parkinson's Disease

Questions	Exposed/ cases	Exposed/ controls	Odds ratio	Signifi- cance
Ever worked in an orchard?	14/57	12/122	2.98	.005
Ever worked in a planer mill?	8/57	4/122	4.82	.004
Ever been involved in chemical spraying?	6/53	2/106	6.64	.005
Ever had the 1918–1919 influenza?	6/57	3/111	4.24	.017
Ever smoked?	30/55	83/120	0.54	.079
Ever handled any of certain chemicals?[a]	31/57	57/121	1.34	.184

[a]These chemicals include glyphosate, picloram, formaldehyde, malathion, 2,4-D, tebuthiuron, paraquat, diazinon, atrazine, pyrethrum, diquat, and bromacil.

the diagnosis of PD, a neurologist (BS) examined all patients in their homes during a 2-week period in August 1988. Fifty-five met generally accepted diagnostic criteria for PD, 4 had possible PD, 6 had essential tremor, 2 had dementia, and 2 had other diagnoses.

We randomly selected controls from regional electoral rolls. Previous checks had indicated that at least 92% of the local population are on the rolls, so the opportunities for bias were minimized. We contacted controls by letter and asked them to complete the questionnaire if they were over 50 years of age. A total of 129 controls completed the questionnaire, giving a response rate of 78%. The controls did not undergo a neurological examination.

Statistical analyses were carried out on only those cases and controls between 50 and 79 years of age. Those aged 80 years or more were excluded for three reasons: (1) we considered that there was inadequate diagnosis beyond 79 years of age: 7 of 13 cases in the 80+ age group had diagnoses other than PD, compared with 3 of 57 below age 80; (2) we were concerned about the recall capability of those over 79 years of age; and (3) we wished to reduce the possibility of including cases related to the 1918–1919 influenza epidemic.

The analysis involved all 57 cases and 122 controls under 80 years of age. To select potential statistically significant associations between variables, we performed condescriptive, frequency, and cross-tabulation procedures using the statistical package, SPSS:X. We used SAS in logistic multiple regression and stepwise analysis to evaluate several variables simultaneously and to generate odds ratios (OR) for measuring the association between environmental exposures and risk of PD. These statistical techniques were employed to test further the associations that we found; the positive associations that we found after regression increased our confidence that these associations were not due to chance.

RESULTS

In our initial screening of the factors that might be associated with PD, we found the following positive associations based on crude odds ratios: working in an orchard, working in a planer mill, involvement in chemical spraying programs, sustaining the 1918–1919 influenza, and familial tremor (Table I). Smoking appeared to be a protective factor in PD development.

We applied a logistic regression approach to those results which had a significant odds ratio to take account of confounding. Sex had no influence in the regres-

TABLE II. Logistic Regression: Case-Control Study of Parkinson's Disease

	Adjusted for sex and age		Adjusted for age and smoking	
Questions	OR	p	OR	p
Ever worked in an orchard?	4.45	.003	2.30	.030
Ever worked in a planer mill?	3.89	.050	4.97	.026
Ever been involved in chemical spraying?	6.62	.031	2.23	.030
Ever smoked?	0.46	.036	—	—
Ever had the 1918–1919 influenza?	1.55	.588	1.83	.464
	Exposed/ cases	Exposed/ controls	Fisher's p	
Ever handled paraquat?	4/57	0/121	0.01	
Ever diagnosed as having familial tremor?	3/53	0/116	0.03	

sion model; we therefore proceeded to adjust for age and smoking. The odds ratios derived for working in an orchard, working in a planer mill, and being involved in chemical spraying programs were 2.30, 4.97, and 2.23 respectively, while having had the 1918–1919 influenza was not significant (Table II).

Four PD patients and no controls reported paraquat contact. Thus, an odds ratio could not be calculated, but a Fisher's exact test gave a significant probability of 0.01. For the association between PD development and postural tremor, the Fisher's test gave a statistically significant probability estimate of 0.03.

Next, all potentially significant variables were entered into a combined logistic regression analysis in order to identify which ones were independent risk factors (Table III). The odds ratios indicate a positive and statistically significant relationship between the development of PD and having worked in an orchard, as well as a borderline statistically significant relationship between developing PD and having worked in a planer mill. A statistically significant inverse association was observed for smoking and PD development. Chemical spraying was not independent of orchard work and therefore was not entered into the model.

To determine whether an association existed between occupation and PD, jobs and industries were collapsed into major groups using the Standard Occupational and Industrial Classification manuals [Statistics Canada, 1980]. Case and control work histories were compared, but there was no indication of overall occupational predisposition to PD. There were no significant differences between cases and controls with respect to private well water use, carbon monoxide poisoning, or contact with manganese on a daily basis. For one variable—handling or contacting certain chemicals—we grouped together a number of chemicals (glyphosate, picloram, formaldehyde, malathion, 2,4-D, tebuthiuron, paraquat, diazinon, atrazine, pyrethrum, diquat, and bromacil); however, this variable was not identified as a factor that might be associated with PD. Involvement in chemical spraying programs was also not significant in this analysis.

DISCUSSION

From a case control study of 57 PD patients, we have found a significant association between developing PD and working in orchards and planer mills. Other researchers have found a correlation between disease incidence and wood processing

TABLE III. Logistic Regression Model (Age-Adjusted): Case-Control Study of Parkinson's Disease

Questions	Odds ratio	p	95% Confidence interval
Ever worked in an orchard?	3.69	.012	1.34, 10.27
Ever smoked cigarettes?	0.40	.019	0.19, 0.86
Ever worked in a planer mill?	4.11	.065	0.91, 18.50

mills and industrial areas [Comella et al., 1987], and it may be that industrial chemicals used in planer mills and orchards, including pesticides, fungicides, and antisapstain agents, are causal factors in PD development.

Paraquat has been suggested as a causal factor of PD [Barbeau et al., 1985; Bus et al., 1976], and Bocchetta and Corsini [1986] reported 2 patients believed to suffer from paraquat-induced parkinsonism. By contrast, Koller [1986] did not find any evidence that paraquat was the cause of PD. In our study, 4 cases and no controls reported "having handled or contacted paraquat." Three of the four cases first used or contacted paraquat within 10 years of their PD diagnosis. For the fourth case, paraquat was originally contacted 28 years before the diagnosis of PD. Researchers have suggested that environmental damage (e.g., exposure to paraquat) remains subclinical for several decades [Calne et al., 1986]; our findings suggest that if paraquat were a causal factor, the damage might occur only a decade before diagnosis or that some damage may occur early in life, and subsequent exposure to paraquat, serves to bring out PD.

We used the odds ratio estimates for working in an orchard, working in a planer mill, and handling paraquat (Table III) and calculated that approximately 15 more cases were found to have had at least 1 of the exposures of interest (i.e., either working in an orchard, working in a planer mill, or handling paraquat) than would have been expected on the basis of the controls. Thus, if the associations found in this research were confirmed in future studies, approximately one fourth of cases might be considered to be "attributable to" the environmental exposures identified here. Tanner et al. [1989] reported results from a study of risk factors for PD in China. They reported finding an increased risk among subjects exposed to industrial chemicals as a broad category, but were no more specific. Although they did not demonstrate an increased risk associated with farming, they point out that Chinese villages have not been exposed to agricultural chemicals until very recently.

The association that we found between planer mill chemicals and PD is interesting, and it would be useful to study the role that specific chemicals may play in PD development. We should consider antisapstain agents such as chlorophenols, which have long been a concern in British Columbia. In addition, we should investigate dithiocarbamates, a common group of fungicides, which Hoogenraad has suggested may be causal factors in PD [1988].

The inverse relationship between smoking and PD has been noted by others [Kessler and Diamond, 1971; Marttila and Rinne, 1980; Duvoisin et al., 1981; Kondo, 1984; Ward et al., 1983; Bharucha et al., 1986]. Some investigators have suggested that substances such as carbon monoxide or 4-phenylpyridine contained in cigarette smoke might exert a protective effect on the brain by reducing the number of free radicals or by acting against the dopamine-depleting effects of MPTP [Irwin

et al., 1987]. In addition to our study, Tanner et al. [1989] showed a decreased but not statistically significant odds ratio among smokers in the development of PD. The apparent protective effect, however, may be misleading. Smoking is less frequent in women, yet the incidence of Parkinson's disease is the same. In addition, the amount of cumulative nicotine exposure in smokers in whom PD occurs is no different to their smoking controls [Haack et al., 1981]. An alternative explanation for the observed difference in smoking may lie in differences in the premorbid personality, creating a tendency to smoke in those who go on to develop PD.

A concern in studies of this type is recall bias. Cases may have considered their chemical exposures and work histories more carefully than controls, or memory for some past events might be impaired as a result of the disease or the patient's age. Fortunately, however, cases should not have been sensitized to the hypothesis that an environmental toxin may be related to PD development because the idea has not gained widespread recognition in the public press. Furthermore, the questionnaire was designed so that chemical exposure questions were integrated with a number of other more general questions to avoid emphasizing any particular field of concern. Also, Elwood et al. [1986] pointed out that, in relationship to studies of fluorescent light exposure and malignant melanoma, postal questionnaires have tended to produce negative results, while interviewer-administered questionnaires have tended to confirm the association. This finding would suggest that postal questionnaires are not susceptible to biases that may be introduced by an interviewer. Other evidence for the credibility of these results includes the fact that a telephone reliability check revealed that the postal questionnaire responses of both cases and controls were equally accurate and complete. Also, finding the "protective effect" of smoking shows that the results were consistent with past findings.

While this study does not demonstrate that orchard or planer mill work "cause" PD, it focusses our attention on the potential PD risk factors associated with certain aspects of these activities. We have gone from previous work suggesting a rural predominance and now we can suggest a concentration in orchards and planer mills. A more thorough study of specific orchard and planer mill exposures is needed on a larger sample, and efforts need to be made to validate self-reports of chemical exposures using independent data sources.

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